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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/905,056 | 07/12/2001 | Avi Ashkenazi | 10466/81 | 2902 |

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EXAMINER

KEMMERER, ELIZABETH

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/905,056 | ASHKENAZI ET AL. |
| | Examiner | Art Unit |
| | Elizabeth C. Kemmerer, Ph.D. | 1646 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 23 February 2004.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 39-47 and 49-51 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) 44-47 and 49-51 is/are allowed.
 6) Claim(s) 39-43 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____

5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment of 23 February 2004 has been entered in full. Claims 1-38 and 48 are canceled. Claims 39-47 and 49-51 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 50 and 51 under 35 U.S.C. § 112, first paragraph, as set forth at pp. 3-5 of the previous Office Action (mailed 21 November 2003) is *withdrawn* in view of the amended claims (submitted with the amendment of 23 February 2004). Also, the issue regarding enablement of the extracellular domain, set forth at the paragraph bridging pp. 4-5 of the previous Office Action (mailed 21 November 2003) is *withdrawn* in view of Applicant's arguments (submitted with the amendment of 23 February 2004).

35 U.S.C. § 112, First Paragraph

Claims 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO: 292 or the mature form or the extracellular domain thereof, which isolated polypeptide has the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in

endothelial cells, does not reasonably provide enablement for other variants of SEQ ID NO: 292. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pp. 3-5 of the previous Office Action (mailed 21 November 2003).

Applicant's arguments in the amendment of 23 February 2004 have been fully considered but are not found to be persuasive for the following reasons.

Applicant argues that the positive reaction obtained in the skin vascular permeability assay (Assay 64) establishes enablement for the claimed polypeptides. Applicants argue that PRO331 caused an inflammatory reaction, that such inflammatory reactions have been used to characterize cytokines such as IL-8, and that thus PRO331's can be used as a target for the development of anti-inflammatory agents. Applicant concludes that because PRO331 caused a specific inflammatory reaction, that agents can be developed for treating inflammation using PRO331, thus meet the enablement provision of 35 U.S.C. § 112, first paragraph. This argument has been fully considered but is not deemed persuasive because one skilled in the art would still not be guided as to how to use the claimed polypeptides. The vascular permeability assay merely establishes is that the substance applied is an irritant. While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one, necessitating substantial further research to determine how to use the compound. For example, the Rampart

reference (Am. J. Pathol. 135:21, 1989) cited by Applicant in the response is one in which IL-8 was found to induce plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation. In this specific case, human PRO331 was found to be an irritant to guinea pigs. Such *might* indicate that PRO331 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO331, e.g. that the human PRO331 protein has an epitope that the guinea pigs were pre-sensitized to. In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO331. Accordingly, the only inflammation that could be treated using anti-PRO331 agents at the time the invention was made is that actually caused by PRO331, which is a circular exercise with no meaning (as there is no reason to believe that any patient has any condition resulting from excess PRO331 based upon the results in the specification as originally filed). It remains that the skin vascular

permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptides.

Applicant stresses that the involvement of neutrophils in the assay clearly demonstrates that PRO331 meets the criteria of a pro-inflammatory molecule and not that of an allergen. This is not found to be persuasive, because the specification does not clearly disclose that the reaction to PRO331 was, in fact, mediated by neutrophils. The assay states, “[s]ites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells **may be** neutrophilic, eosinophilic, monocytic **or** lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative” (emphasis added). Thus, the specification does not disclose that PRO331 clearly induced a neutrophil-mediated inflammatory response.

Conclusion

Claims 44-47 and 49-51 are allowable. Claims 39-43 are not allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne L. Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK



ELIZABETH KEMMERER
PRIMARY EXAMINER